1 Introduction

Craniofacial anomalies (CFA) are a highly diverse group of complex congenital anomalies. Collectively they affect a significant proportion of the global society *(see Table 1 below)*.

Table 1: Examples of most common craniofacial anomalies

	Prevalence at birth: per 10 000
Cleft lip ± palate	
Caucasian	10
Japanese	20
Native (North) Americans	36
African American population	3
Cleft palate	
Averaged across races	5
Craniosynostosis	3
Crouzon syndrome	0.4
Apert syndrome	0.15
Otomandibular anomalies	1.2
Treacher Collins syndrome	0.2
CHARGE Association	1
Holoprosencephaly	1.2
Stickler syndrome	1
Fetal alcohol syndrome	2

Source: Rovin et al., 1964, Temple, 1989; Cohen et al., 1992; Lewanda et al., 1992; Croen et al., 1996; Derijcke et al., 1996; Sampson et al., 1997; Blake et al., 1998.

The prevalence of individual conditions varies considerably across geographic areas and ethnic groupings. Their impact on speech, hearing, appearance and cognition has a prolonged and adverse influence on health and social integration. The costs incurred from CFA in terms of morbidity, health care, emotional disturbance, and social and employment exclusion are considerable for affected individuals, their families and society. Research that will increase the understanding of the causes of CFA, improve the treatment for it, and lead ultimately to its prevention or reduction, has mainly been pursued in the absence of an international strategy. Yet international collaboration is a prerequisite for accessing adequate samples for research in etiology, treatment and prevention, and also for the assembly of a critical mass of clinical researchers and basic scientists in fields such as molecular biology, genetics, biochemistry and epidemiology.

Great confusion surrounds the optimal management for even the most common conditions

The treatment of CFA has, so far, escaped the rigours of contemporary health technology assessment, and great confusion surrounds the optimal management for even the most common conditions. For each of the many subgroups of CFA, the attainment of homogeneous samples of adequate size for randomized trials and long-term follow-up represents a formidable challenge. Multi-site cooperation is essential. In the developing world, the costs of rehabilitation and problems of access put treatment beyond the reach of vast numbers of affected individuals. Systems for delivering care in different geographic and economic circumstances urgently require research.

The potential of research on the genetic basis of CFA has increased dramatically over the last decade with the development of recombinant DNA technology. In over 50 craniofacial syndromes, genes involved have either been mapped to a chromosome location or actively isolated and their structure identified. This achievement, however, represents only a fraction of the total number of craniofacial syndromes defined. The pathogenesis of the most common forms of CFA – non-syndromic clefts of lip and/or palate – is especially challenging because they appear to arise from complex polygenic interactions with environmental factors. A coordinated international approach would not only provide effective means of sharing data, samples and resources, but would allow strategic exploitation of geographic and ethnic variation in the incidence and pathogenesis of CFA.

Research that may lead to the prevention of CFA has been based, primarily, on isolated case control studies in Asia, Europe, Latin America and the United States of America. As yet, these projects have occurred independently of each other, and consistent conclusions about viable interventions such as dietary supplementation in the periconceptual

period have yet to emerge. Once again, international standardization of research protocols, consensus on preventive interventions suitable for clinical trials, and the performance of trials in an international framework, would enhance the validity, consistency and generalizability of these efforts.

Efforts to define an international research strategy go back more than a decade when the proposals for "International Collaboration on Oral Health" were jointly published by WHO, the International Dental Federation (FDI), and the US National Institute for Dental and Craniofacial Research. More recently these proposals were renewed at a series of consensus meetings:

- Eighth Congress of the International Confederation of Craniofacial Teams, Singapore, 1997;
- Craniofacial Genetic Diseases and Disorders Planning Workshop, Bethesda, USA, 1997;
- International Collaboration on Oral Cleft Genetics Second Meeting, Baltimore, USA, 1998; and
- Meeting of the International Task Force on CFA, Bauru, Brazil, 1998.

In 2000, the WHO Human Genetics Programme, with financial support from the US National Institute of Dental and Craniofacial Research, launched a five-year project designed to take these proposals forward. The specific objectives of this initiative have been to develop an international network for consensus building, planning and protocol development for international, collaborative, biomedical, epidemiological and behavioural studies in the core areas of CFA research, and to create a directory of CFA research resources and a publicly-accessible research database on the Internet.

This report is based on the first two consensus meetings of international of experts held under the auspices of WHO. The first meeting, held in Geneva, 5-8 November 2000, included concurrent workshops on research concerning the genetic basis of CFA, gene/environment interactions, and the treatment of CFA. The second meeting, held in Utah, 24-26 May 2001, considered the prevention of CFA.